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Squamous cell carcinoma of the penile skin in a neovagina 20 years after male-to-female reassignment

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SUMMARY. We present a patient who underwent male-to-female reassignment, and then developed squamous cell carcinoma during a complicated long-term follow-up. In very rare cases, squamous cell carcinoma may be considered in the differential diagnosis of sustained ulceration in neovaginas constructed by inverting the penile skin in male-to-female reassignments, in particular because clinical examination may be hampered by contractile scar formation of the neovaginal canal. Despite the lack of statistical evidence, it may be assumed that the heterotopic penile skin is at an increased risk of developing HPV-induced squamous cell carcinoma, especially if, over the years, there is a personal history of venereal warts. © 2002 The British Association of Plastic Surgeons

Keywords: squamous cell carcinoma, penile skin, neovagina, male-to-female reassignment, human papillomavirus.

The inversion of the penile skin is a well-established method of vaginal construction in male-to-female reassignment.[1–3] However, this procedure carries a considerable risk of postoperative complications, including rectovaginal fistulae, ulceration, vaginal or urethral stenosis and abscesses.[4] These complications may result in chronic laceration and infection of the transposed glans or prepuce. Sustained inflammation and chronic ulceration, in the form of fistulae or burn scars, are known to carry the risk of malignant degeneration.[5,6] It is, therefore, conceivable that the heterotopic glans and prepuce may be at increased risk of developing squamous cell carcinoma as a result of environmental factors, especially if there is a personal history of venereal warts, caused by high-risk human papillomavirus (HPV), leading to anogenital and penile malignancies.[7,8] However, because of the limited patient population undergoing reassignment surgery, there is a paucity of data documenting this risk.

Case report

A male-to-female transsexual, with a previous history of chronic venereal warts, had undergone gender reassignment at the age of 24 years. The vagina was constructed using penile and scrotal skin inversion. After an uneventful period of 18 years, the patient presented with an increasing vaginal discharge, which was initially treated with antibiotics for more than 4 weeks. The scar-related tightness of the neovagina did not permit a conclusive manual examination. A vaginoscopy was performed because of the persistence of the disease, and revealed a blind-ending fistula. This was excised, and a swab was taken for cytological examination, which was negative. The discharge persisted, and surgical revision was undertaken 4 months later. Atypical cells were found in the specimen obtained during surgery, which required the excision of the ulcer within the neovagina. Histopathology revealed a moderately differentiated verrucous carcinoma of the formerly inverted penile skin. The presence of pleomorphic and cytoplasmic nuclei (coilocytes) (Fig. 1), combined with the patient's history of condyloma acuminata, made HPV involvement likely. Although immunohistochemistry was negative, the diagnosis was confirmed by polymerase chain reaction (PCR) (Roche Diagnostics GmBH, Roche Molecular Biochemicals, Mannheim, Germany) performed on the ulcer sample, which showed viral genome (Fig. 2). The final diagnosis was, therefore, HPV-induced squamous cell carcinoma of the penis.

Subsequent MRI showed a mass in the posterior wall of the neovagina, with clear demarcation (Fig. 3). Ilioinguinal lymph-node enlargement and skeletal extension were excluded by MRI and bone scintigraphy, respectively.

The tumour was treated by total resection of the neovagina, followed by combined radiotherapy and chemotherapy. Unfortunately, the radiotherapy resulted in the development of rectovaginal fistulae, which required a deviation sigmoidostomy. At follow-up 2½ years after radiotherapy and chemotherapy, the patient was free of recurrence, the fistulae were healed and intestinal continuity was restored.

Discussion

Wound-healing complications, such as abscesses, scar-related vaginal stenoses and urethral strictures, and recto-neovaginal fistulae, are among the most frequent complications of vaginal construction with inverted penile skin.[4,9,10] No metaplastic alterations have been reported in the few long-term follow-up studies.[11–13] To date, the only report of squamous cell carcinoma in the neovagina refers to a patient undergoing vaginal reconstruction with skin grafts after vaginal resection in Mayer-Rokitansky-Kuster-Hauser syndrome.[14] Therefore, to our knowledge, this is the first report of squamous cell carcinoma in penile skin used for vaginal construction.

PCR confirmed that the tumour was infected with HPV, proving persistent HPV infection within the neovaginal tissue. Sexually transmitted HPV infections, in

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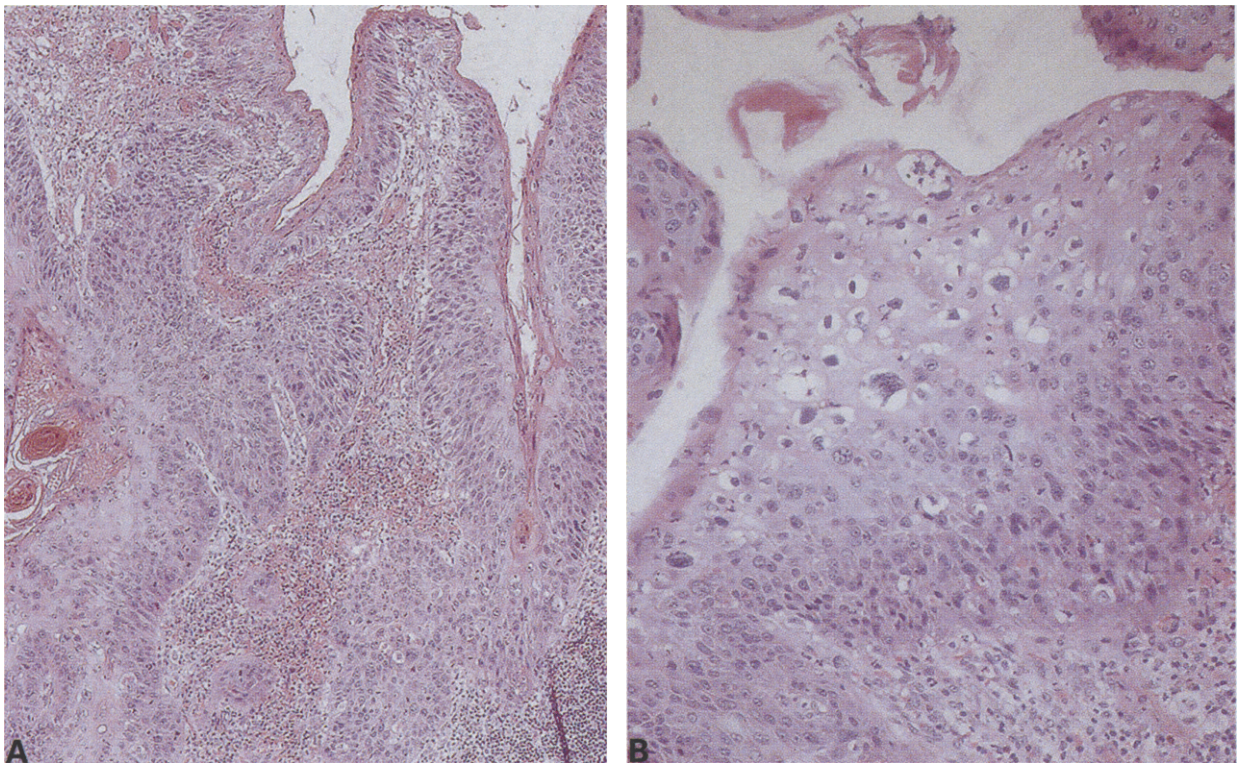

Figure 1—Histological appearance of the squamous cell cancer: (A) overview and (B) cutting with pleomorphic and cytoplasmic nuclei.

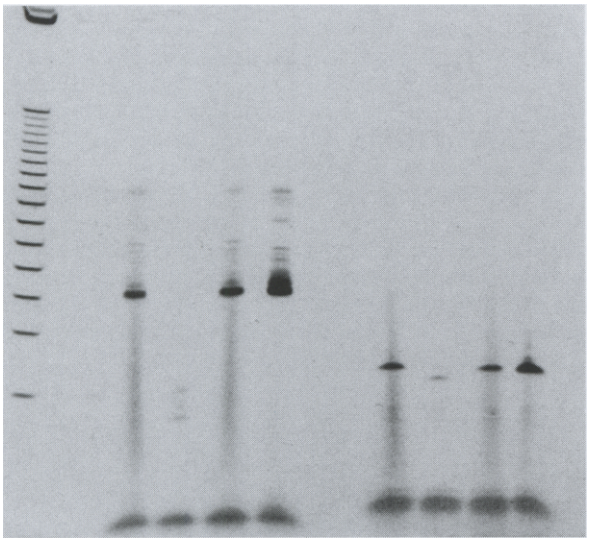

Figure 2—Polymerase chain reaction shows bands of extracted DNA typical of human papillomavirus.

particular those with the high-risk genotypes HPV-16 and HPV-18, play a pivotal role in the development of cervical cancer worldwide.[15] Recently, HPV was also associated with the induction of anal cancer and squamous cell carcinoma of the penis.[8,11,16] Based on this observation, we suggest that HPV played a causal role in the development of this tumour. However, unlike cervical carcinoma, the association of squamous cell carcinoma of the penis with HPV is still controversial. The prevalence of HPV infection in patients with penile carcinoma was reported to be

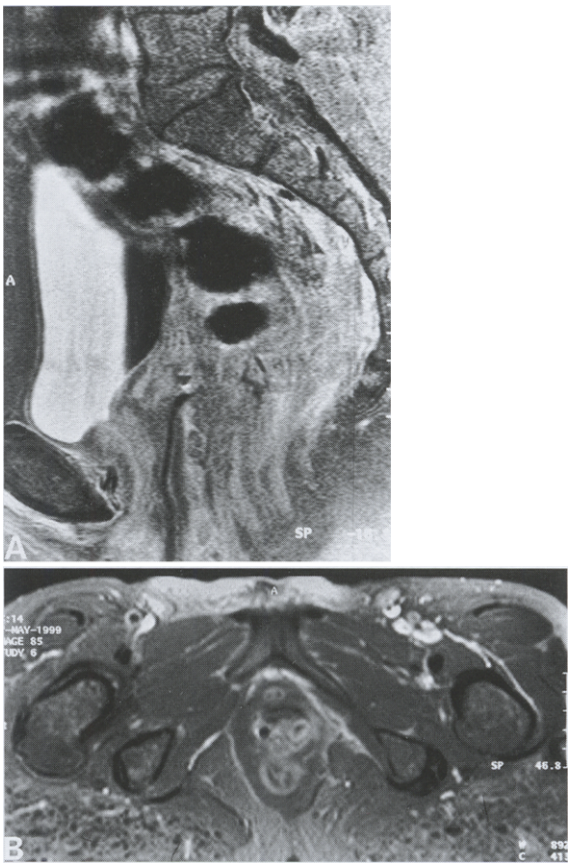

Figure 3—(A) Transverse and (B) coronal MRI, showing a well-described mass with central necrosis.

15% in a Hong Kong population but 71% in an Argentinean investigation.[17,18] These differences in outcome may be explained by racial, climatic and methodological differences. Nevertheless, HPV-induced penile carcinoma seems to affect younger patients and those with a long history of venereal warts, which were both factors in our patient.

Furthermore, Ulfelder reported a distinct histological difference in the epithelial lining of the neovagina between that resulting from spontaneous epithelialisation and that obtained by skin grafting.[19] The histological appearance and staining characteristics of the former were similar to native vaginal epithelium, whereas the grafted skin retained its original features. Further evidence of the difference between grafted and normal vaginal tissue appears in Whitacre and Alden's description of a black female in whom a neovagina was constructed using a full-thickness skin graft.[20] Black pigment was still plainly visible in several regions of the explant 47 weeks after grafting. These reports suggest that transplanted or transposed tissues retain their original characteristics. It may, therefore, be assumed that these tissues also maintain their oncological potential. We wonder whether heterotopic skin of the glans and prepuce is exposed to an increased risk of malignant degeneration as a result of the moist environment in the neovaginal canal. To date, no clear environmental factor has been described for the development of cancer in the vagina. Nevertheless, Cromer attributed the genesis of anogenital epithelial malignant transformation to a so-called unspecific field effect from an as yet unidentified carcinogen or mutagen, which may be related to an environmental factor.[21]

Based on a case report, Lathrop et al stated that reduction of sexual contact could limit the exposure of a patient to presumably oncogenic stimuli, such as HPV and herpes simplex virus type 2.[22]

In conclusion, our report emphasises that, in very rare cases, squamous cell carcinoma may be considered in the differential diagnosis of sustained ulcerations in neovaginas constructed by inverting the penile skin in male-to-female reassignments, in particular because clinical examination may be hampered by contractile scar formation of the neovaginal canal. Despite the lack of statistical evidence, it may be assumed that the heterotopic penile skin is at an increased risk of developing HPV-induced squamous cell carcinoma.

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